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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/930,020	08/14/2001	Kurt C. Gish	05882.0168.CPUS01	2304

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EXAMINER	
RAWLINGS, STEPHEN L	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 06/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/930,020	GISH ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32,38-40,42,43 and 45-68* is/are pending in the application.

4a) Of the above claim(s) *60-68* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32,38-40,42,43 and 45-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20041221; 20050317*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 15, 2005 has been entered.

1. The amendment filed March 15, 2005 is acknowledged and has been entered. Claim 44 has been canceled. Claims 32, 50, and 57 have been amended.

2. Claims 32, 38-40, 42, 43, and 45-68 are pending in the application. Claims 60-68 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

3. Claims 32, 38-40, 42, 43, and 45-59 are currently under prosecution.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

5. The information disclosures filed December 21, 2004 and March 17, 2005 have been considered. An initialed copy of each is enclosed.

Grounds of Objection and Rejection Withdrawn

6. Unless specifically reiterated below, Applicant's amendment and/or arguments set forth in the amendment filed March 15, 2004 have obviated or rendered moot the

grounds of objection and rejection set forth in the previous Office action mailed November 15, 2004.

Grounds of Rejection Maintained

Claim Rejections - 35 USC § 101

7. The rejection of claims 32, 38-40, 42, 43, and 45-59 under 35 U.S.C. § 101, because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility for the reason set forth in section 8 of the preceding Office action mailed November 15, 2004 is maintained.

At pages 5 and 6 of the amendment filed March 15, 2004, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Applicant has argued that Table 1 lists the gene that were found to be over-expressed in colorectal cancer cells and that "Applicants' internal reference number 'W07459' associated with the gene encoding the polypeptide of SEQ ID NO:2 may be found as the seventh entry listed on Table 1" (page 6, paragraph 1). Furthermore, Applicant has asserted, "the disclosure makes it readily apparent to one of ordinary skill in the art that differential expression of CBF9 may be used as a diagnostic for colorectal cancer" (page 6, paragraph 1).

The Examiner disagrees with Applicant's assertion that the disclosure makes it readily apparent to one of ordinary skill in the art that differential expression of CBF9 may be used as a diagnostic for colorectal cancer, because, as explained in the preceding Office actions, the specification does not teach whether the gene encoding the CBF9 polypeptide of SEQ ID NO: 2 is over- or under-expressed in colorectal cancer cells, as compared to normal colorectal cancer cells.

In reply to the first Office action on the merits, Applicant argued that the disclosure implies the gene encoding the CBF9 polypeptide of SEQ ID NO: 2 is overexpressed in colorectal cancer. This argument was not found persuasive because, while Table 1 lists the genes that Applicant found to be overexpressed in colorectal

cancer cells, the gene encoding CBF9 (Unigene No. Hs.157601; GenBank™ Accession No. AC05383) does not appear to be included in this list and therefore the specification does not explicitly teach whether the gene encoding CBF9 is overexpressed in colorectal cancer cells.

In response to the preceding final Office action, Applicant has now argued that Table 1 does indeed list the gene encoding the CBF9. In particular, Applicant has asserted that this gene is listed in the Table at page 1 in the seventh row.

In accordance with the legend at page 68, row 7 of Table 1 lists the following information:

"Primekey (unique probeset identifier)":	322303
"Exemplar" Accession Number:	EOS22234
"EOS Code Number":	W07459
UniGene™ Accession Number:	(not in UniGene).

In contrast, the sequence of the complementary DNA (cDNA) encoding CBF9, which is set forth in Table 2, identifies the sequence using the following information:

UniGene™ Accession Number:	Hs.157601
"Probeset" Accession Number:	W07459
Nucleic Acid Accession Number:	AC005383
Coding Sequence:	328-2751.

The only common information in the tables that might, at first glance, appear to provide a cross-reference to support Applicant's allegation that the disclosure makes it readily apparent to one of ordinary skill in the art that differential expression of CBF9 may be used as a diagnostic for colorectal cancer is "W07459"; however, in Table 1, "W07459" is identified as a "EOS Code Number", whereas in Table 2 it is identified as a "Probeset Accession Number".

While Applicant has stated that W07459 is "Applicants' internal reference number" identifying the gene encoding CBF9, Table 2 does not describe the gene identified in row 7 as the gene encoding CBF9, nor does it describe the gene as comprising the nucleotide sequence set forth as SEQ ID NO: 1, or as encoding the amino acid sequence set forth as SEQ ID NO: 2.

Furthermore, while the gene encoding CBF9 is identified in Table 2 by the UniGene™ Accession Number, Hs.157601, the gene described in row 7 of Table 1 is not identified by a UniGene™ Accession Number, as the table indicates the gene is not contained in the UniGene™ database.

These discrepancies have not been explained.

In actuality it appears that Table 1 lists the EST clones that were found to be over-represented in colon cancer specimens that Applicant analyzed. W07459 is the accession number used in GenBank™ database to identify a 241 bp EST clone isolated from human fetal lung. The clone maps to a transcribed locus that is identified in the UniGene™ database as Hs.389988, a gene-oriented cluster that has so far been linked to 12 different EST clones. According to the UniGene™ database, Hs.389988 maps to a sequence-tagged site, which is identified in the UniSTS database as D11S4421. D11S4421 maps to chromosome 11 at position 11q23.3.

As explained in the preceding Office action, the nucleic acid encoding CBF9 is identified using GenBank™ Accession Number AC005383; however, the nucleic acid sequence referred to by this accession number is 1,217,714 nucleotides in length and the nucleic acid sequence disclosed as SEQ ID NO: 1 and encoding CBF9 (SEQ ID NO: 2) is only 3,375 nucleotides in length. Notably, Applicant has addressed this apparent discrepancy, stating at page 6 of the amendment filed March 15, 2005 that the nucleotide sequence of SEQ ID NO: 1 is found within the larger sequence. However, the sequence of SEQ ID NO: 1 is the sequence of a complementary DNA (cDNA) molecule and the sequence set forth under GenBank™ accession number AC005383 is the sequence of a genomic DNA molecule. The sequence of a cDNA molecule will not be found in the sequence of a genomic DNA molecule, because the latter comprises intervening sequences (i.e., introns), which are interspersed among the coding

sequences (i.e., exons). The cDNA molecule is produced using a mature messenger RNA (mRNA) molecule, which lacks these intervening sequences, and so comprises only the contiguous sequences of the spliced coding sequences. Nevertheless, the genomic sequence set forth under GenBank™ accession number AC05383 is the sequence of a portion of chromosome 10. As noted above, the EST clone having the GenBank™ accession number W07459 does not map to chromosome 10, as it maps to chromosome 11.

In light of the multitude of discrepancies, contrary to Applicant's assertion, it is submitted that the specification does not explicitly teach whether the gene encoding CBF9 is overexpressed in colorectal cancer cells and moreover, the disclosure does not make it readily apparent to one of ordinary skill in the art that differential expression of CBF9 may be used as a diagnostic for colorectal cancer.

Claim Rejections - 35 USC § 112

8. Claims 32, 38-40, 42, 43, and 45-59 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility for the reasons set forth in the section above, one skilled in the art clearly would not know how to use the claimed invention.

Furthermore, as noted in the preceding Office action, if the grounds of rejection of the claims under 35 USC § 101 set forth in the section above were to be obviated, claims 32, 38-40, 42, 43, and 45-59 would still be rejected under 35 U.S.C. 112, first paragraph, because there is a preponderance of factual evidence of record that the skilled artisan could not use the claimed invention without undue experimentation. The claims are drawn to a method for diagnosing colorectal cancer comprising measuring and comparing the level of a polynucleotide encoding a CBF9 polypeptide, which is "an RNA equivalent of a nucleic acid sequence at least 90% identical to the nucleic acid sequence disclosed from nucleotide 328 to 2751 of SEQ ID NO: 1. Table 1 does not teach that members of such a genus of structurally variant nucleic acid molecules are overexpressed in colorectal cancer, relative to normal colorectal tissue, and could

therefore be used to differentiate colorectal cancer cells from normal colorectal cells. Were any member of the genus to be diagnostic of colorectal cancer, it would require undue experimentation to determine its identity.

9. The rejection of claims 32, 38-40, 42, 43, and 45-59 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

At pages 7-9 of the amendment filed March 15, 2004, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, "Written Description" Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

Applicant has argued that Fetrow et al. teaches, "predicting function is only problematic once there is no longer a certain threshold of sequence similarity" (page 9, paragraph 1). Applicant has submitted provided there is enough sequence similarity between the sequences of two proteins, assigning a function to a protein similar to another having a known function is not problematic. Because the claims are drawn to the members of a genus of polypeptides that are the RNA equivalents to a nucleic acid sequence at least 90% identical to the nucleic acid sequence from nucleotide 328 to 2751 of SEQ ID NO: 1, Applicant has apparently asserted that having described the nucleotide sequence of SEQ ID NO: 1, the written description requirement has been met.

Whether or not the art teaches it is possible to accurately assign a function to a protein merely upon the basis of an observed structural similarity to another protein of known function could be debated. However, the question, here, is not whether it is possible to accurately infer the function of a novel protein from its similarity to another protein, but whether or not its similarity to another protein might infer that it, like its homolog, is associated with colorectal cancer. Moreover, the question, here, is whether or not the supporting disclosure would reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

The claims are directed to a genus of nucleic acid molecules that are diagnostic (i.e., aberrantly expressed in colorectal cancer cells, as compared to normal colorectal cells, so as to enable their distinction). Table 1 lists 1,747 different EST clones that were found to be over-represented in specimens of colorectal cancer, relative to some other reference tissue or cells. However, as explained above, it does not appear that Table 1 lists the nucleic acid molecule of SEQ ID NO: 1.

Nevertheless, there is an assertion that the RNA equivalent of the nucleic acid of SEQ ID NO: 1 is over-expressed in colorectal cancer cells, as compared to normal colorectal tissue, as in claim 1, for example. Claim 1, however, further asserts that other structurally disparate nucleic acid molecules, which are the RNA equivalents of a nucleic acid sequence at least 90% identical to the nucleic acid sequence of SEQ ID NO: 1, are also over-expressed in colorectal cancer; but the specification only adequately describes the RNA equivalent of the nucleic acid of SEQ ID NO: 1. As evidenced by Skolnick et al., one cannot accurately infer the function of a protein on the basis of a favorable comparison of its amino acid sequence to the amino acid sequence of another protein having a known function. While it is again noted that Applicant has traversed this point, even if it might be possible to predict the function of a protein by such comparison, it is submitted that it is not possible to predict whether any protein is over-expressed in colorectal cancer, relative to normal colorectal tissue, regardless of the structural, and even functional similarity it may have to another protein.

Although the polypeptide of SEQ ID NO: 2 may be eventually be found to be overexpressed in colon cancer, the skilled artisan cannot predict which of the other

polypeptides encoded by the RNA equivalents of a nucleic acid sequence at least 90% identical to the nucleic acid sequence of SEQ ID NO: 1 are also overexpressed in colon cancer. Even among closely related protein family members, the skilled artisan cannot predict whether a particular member of the family is associated with the etiology or pathology a specific disease, solely on the basis that another member of the family has been shown to be. De Plaen et al. (*Immunogenetics.* 1994; **40**: 360-369), for example, reviews the structure, chromosomal localization and expression of twelve genes encoding members of the MAGE family of proteins; see entire document (e.g., the abstract). De Plaen et al. teaches six of the members of the gene family were found to be expressed at a high level in a number of tumors of various histological types; while five were very weakly expressed in all samples tested, and one, namely MAGE 7, was not transcribed at all in the ninety-five tumor samples tested (page 367, column 1). Just as not all members of the MAGE family of proteins are associated with cancer, particularly, since is it not obvious what, if any, association the weakly expressed MAGE proteins have, it is apparent that the skilled artisan cannot predict, based upon the information disclosed in the specification, whether variants of the polypeptide of SEQ ID NO: 2, as members of a presumed family of structurally related proteins, have an association with the etiology or pathology of colon cancer (e.g., whether the genes encoding such variants are overexpressed in colon cancer). The Federal Circuit has decided that a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. See *Noelle v. Lederman*, 69 USPQ2d 1508 1514 (CA FC 2004) (citing *Enzo Biochem II*, 323 F.3d at 965; *Regents*, 119 F.3d at 1568).

Furthermore, "generalized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004). In this instance, there is no language that adequately describes the RNA equivalents to which the claims are drawn that can be used to achieve the claimed diagnostic result. A description of what a material does, or

how it is expressed, rather than of what it is, does not suffice to describe the claimed invention.

"Regardless whether a compound is claimed *per se* or a method is claimed that entails the use of the compound, the inventor cannot lay claim to the subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods". *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1894 (CAFC 2004). The claimed method depends upon finding RNA equivalents of a nucleic acid that is 90% identical to the nucleic acid of SEQ ID NO: 1, which is over-expressed in colorectal cancer cells, relative normal colorectal tissue, to achieve a diagnostic result; without such nucleic acids, it is impossible to practice the invention.

Although the skilled artisan could potentially identify such RNA molecules that might be used in practicing the claimed invention by performing differential expression analyses, it is duly noted that the written description provision of 35 U.S.C § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (CAFC 1991). See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993); *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016 (CAFC 1991); *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

Finally, Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description'' Requirement (66 FR 1099-1111, January 5, 2001) states, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the

invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Moreover, because the claims are directed to a genus of RNA molecules, which vary both structurally and functionally, despite being commonly over-expressed in colorectal cancer, relative to normal colorectal tissue, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. In this instance, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; Applicant has not shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; and Applicant has not described distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention at the time the application was filed.

Conclusion

10. No claims are allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
May 26, 2005